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DIAGNOSIS, RISK FACTORS AND QUALITY-OF-LIFE IN PATIENTS WITH MYOCARDIAL INFARCTION AND NORMAL CORONARY ARTERIES

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DIAGNOSIS, RISK FACTORS AND QUALITY-OF-LIFE IN PATIENTS WITH MYOCARDIAL INFARCTION AND NORMAL CORONARY ARTERIES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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"Perplexity
is the
beginning
of knowledge"

Khalil Gibran

To everyone, but most to my son Joel

ABSTRACT

***Background*:** Myocardial infarction with normal coronary arteries (MINCA) is a common condition that mostly affects middle-aged women. The pathogenesis is complex and includes various mechanisms that need to be explored for appropriate diagnosis and treatment. Patients with MINCA often complain about low energy and appear to be distressed. Previous studies in MINCA with control groups were lacking when the Stockholm myocardial infarction and normal coronaries (SMINC) study started.

***Aims*:** To describe cardiac magnetic resonance (CMR) imaging findings, background characteristics, atherosclerosis markers and quality-of-life (QoL) in patients with MINCA. The intention is to better understand and improve the management of this group of patients.

***Specific aims, methods and results*:**

Study I: The aim was to report the true prevalence of myocarditis and MINCA with or without myocardial infarction by using CMR. We investigated 152 patients 35-70 years and found that 67% had a normal CMR, 19% had signs of myocardial necrosis and 7% had signs of myocarditis. Twenty-two percent of all MINCA with a normal CMR fulfilled the Mayo clinical diagnostic criteria for TS. The CMR was performed a median of 12 days (6-28 days) after the acute event.

Study 2: The aim was to describe the risk factors by analysing the case record form (CRF) and different investigations performed during the 3 months follow up after the acute event in patients with MINCA and compare those with two control groups. We analysed blood samples, reactive hyperaemia index (RHI) and intima-media thickness (IMT) by using EndoPAT® (Itamar Medical Ltd) and ultrasound of the carotids. The results showed that MINCA was associated with similar risk factors as in coronary heart disease (CHD) patients except for a more favourable lipid profile. The atherosclerotic burden in MINCA, measured as RHI and IMT, were within the normal range and similar to both healthy and CHD controls. Psychiatric disorders were more common in patients with MINCA and TS than those without TS and more than half of all MINCA patients recalled physical and emotional stress before admission.

Study 3: The aim was to describe the physical capacity and QoL 6 weeks to 3 months after the acute event in MINCA compared to both control groups using an exercise bicycle stress test and Short Form (SF)-36. The findings showed that patients with MINCA had a lower exercise capacity and QoL compared with healthy controls. Compared with CHD controls the results showed better exercise capacity in MINCA but lower mental and vitality scores in the mental component of SF-36, otherwise the dimensions were similar.

Study 4: The aim was to evaluate mental health in MINCA patients and compare them with two control groups by using two different surveys 3 months after the acute event; the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression scale (HADS). Our findings showed that anxiety and depression were common with prevalence rates similar to patients with CHD. Anxiety was more common in patients with MINCA and TS than those without TS.

Conclusions: CMR imaging is an important tool that can help us to identify the different underlying diagnoses in MINCA and enable a more adequate treatment. Patients with MINCA do not have signs of early or generalized atherosclerosis and they share a number of cardiovascular risk factors with patients who have CHD, including high prevalence of anxiety and depression. There is also a decline in QoL similar to that of CHD patients and in some perspectives even worse in the domain of mental health. Altogether these findings show a high vulnerability to mental stress in patients with MINCA. The lack of clarity regarding diagnosis and treatment can also increase the stress and therefore highlight the need for a change in the management care of patients with MINCA, not only in the hospital but also after being discharged. Performing CMR early (2 weeks from presentation) and follow-up care in in a similar way as in patients with CHD will probably decrease the mental stress and improve QoL.

LIST OF SCIENTIFIC PAPERS

I. Collste O*, Sorensson P*, Frick M, Agewall S, Daniel M, Henareh L, Ekenbäck C, Eurenius L, Guiron C, Jernberg T, Hofman-Bang C, Malmqvist K, Nagy E, Arheden H and Tornvall P. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. Journal of internal medicine. 2013;273(2):189-96. *shared first author.

II. Daniel M*, Ekenbäck C,* Agewall S, Brolin EB, Caidahl K, Cederlund K, Collste O, Eurenius L, Frick M, Y-Hassan S, Henareh L, Jernberg T, Malmqvist K, Spaak J, Sörensson P, Hofman-Bang C and Tornvall P. Risk Factors and Markers for Acute Myocardial Infarction with Angiographically Normal Coronary Arteries. Am J Cardiol. 2015;116(6):838-44. *shared first author.

III. Daniel M, Agewall S, Caidahl K, Collste O, Ekenbäck C, Frick M, Y- Hassan S, Henareh L, Jernberg T, Malmqvist K, Schenck-Gustafsson K, Sörensson P, Sundin Ö, Hofman-Bang C and Tornvall P. Effect of Myocardial Infarction with Non-Obstructive Coronary Arteries on Physical Capacity and Quality-of-Life. Am J Cardiol. 2017; 120:341-346.

IV. Daniel M, Agewall S, Berglund F, Caidahl K, Collste O, Ekenbäck C, Frick M, Henareh L, Jernberg T, Malmqvist K, Schenck-Gustafsson K, Spaak J, Sundin Ö, Sörensson P, Y-Hassan S, Hofman-Bang C, Tornvall P. Prevalence of Anxiety and Depression Symptoms in Patients with Myocardial Infarction with Non-Obstructive Coronary Arteries. Am J Med. 2018;131(9):1118-24.

CONTENTS

List of abbreviations

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARB	Angiotensin renin blocker
BDI	Beck's depression inventory
CAS	Coronary artery spasm
CAD	Coronary artery disease
CRF	Coronary flow reserve
CHD	Coronary heart disease
CMVD	Coronary microvascular dysfunction
CMR	Cardiac magnetic resonance
CRF	Case record form
CT	Computed tomography
ECG	Electrocardiography
EMB	Endomyocardial biopsy
EndoPAT	Endovascular and peripheral and arterial tone
Gd	Gadolinium
HADS	Hospital anxiety and depression scale
IGT	Impaired glucose tolerance
IMT	Intima media thickness
IVUS	Intravascular ultrasound
LGE	Late gadolinium enhancement
LV	Left ventricle
MB	Myocardial bridging
MRI	Magnetic resonance imaging
MINCA	Myocardial infarction with normal coronary arteries
MINOCA	Myocardial infarction with non-obstructive coronary arteries
NO	Nitric oxid
NT-pro-BNP	N-terminal prohormone brain natriuretic peptide
OCT	Optical coherence tomography
PD	Plaque disruption
PE	Pulmonary embolism
MCS	Mental component summary
PCS	Physical component summary
QoL	Quality-of-life
SCAD	Spontaneous coronary artery dissection
SF36	Short form (36) health survey
SMINC	Stockholm myocardial infarction with normal coronaries
STEMI	ST-elevation myocardial infarction
TS	Takotsubo syndrome

INTRODUCTION

During the last century several medical developments have been introduced in our cardiac clinics with the aim of improving health and reducing mortality. The first portable ECG machine was introduced in the beginning of last century and the first coronary care unit was established in Scotland 1964 [1]. When the era of coronary angiography and percutaneous coronary interventions started 50 years ago, non-obstructed coronary arteries in patients with acute myocardial infarction (AMI) was considered as a benign condition and the focus was to prevent and treat patients with obstructed coronary arteries. The cause of "normal" coronary arteries was thought to be spontaneous reperfusion, missed coronary artery lesion, coronary spasm or secondary due to other reasons such as anaemia [2]. In past decades myocardial infarction with non-obstructive coronary arteries (MINOCA) has been recognized due to sensitive troponin assays and increased number of coronary angiograms performed after AMI [3]. Compared to patients with obstructed coronary arteries, patients with MINOCA are younger and women are more affected [4]. In general the prognosis is relatively good compared to patients with obstructed coronary arteries but recent long-term mortality data after coronary angiogram showed that one-third of deaths occurred in women without obstructive coronary arteries [5]. There are large gaps of knowledge regarding etiology, diagnosis and treatments in MINOCA syndrome. Patients also appear to have difficulties in coping with their new situation and many of them are reporting anxiety and lack of physical and mental energy for a prolonged time after leaving the hospital. Some possible reasons for this could be medical uncertainty regarding diagnosis or lack of follow-up care similar to patients with obstructed coronary arteries [6,7].

BACKGROUND

DEFINITION OF MINCA AND MINOCA

Previously researchers often used the name myocardial infarction with normal coronary arteries (MINCA) and the syndrome had a stricter definition with no or minor endo-luminal irregularities without stenosis [8]. The first international expert paper about the condition was presented in the European Heart Journal and the diagnostic criteria for MINOCA included the presence of AMI criteria and no coronary artery stenosis ≥50% in any potential infarct-related coronary artery on angiography and with no other obvious clinical cause [9]. The authors concluded that the term MINOCA should only be used as a "working diagnosis" in the evaluation of a suspected AMI. The Third Universal Definition of Myocardial Infarction, defined the criteria as increased cardiac markers of myocardial injury and showing at least one of the following: ischemic symptoms, significant ST-T changes, new left bundle branch block, development of pathological Q-waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities, intracoronary thrombus evident on coronary angiography or at autopsy [10].

EPIDEMIOLOGY

MINOCA is a common diagnosis with a prevalence ranging from 1%-15% depending on studied population, thresholds for coronary angiography and the definition of coronary artery stenosis [11-19] (Table 1). According to a recent published meta-analysis the prevalence of MINOCA was approximately 6% (95% confidence interval (CI), 5%-7%) of all AMI and 40% were women [4]. These studies revealed all-cause in-hospital and 12-month mortality of 0.9% (95% CI, 0.5%-1.3%) and 4.7% (95% CI, 2.6%-6.9%), respectively. In Sweden, statistics from The National Board of Health and Welfare showed almost 27,000 cases of AMI in 2016, corresponding to 352 cases per 100,000 inhabitants and year and with a mortality of 25% within 28 days, (http://www.socialstyrelsen.se/publikationer2017/2017-10-24). We estimated at least 21 cases of MINOCA per 100,000 inhabitants and year.

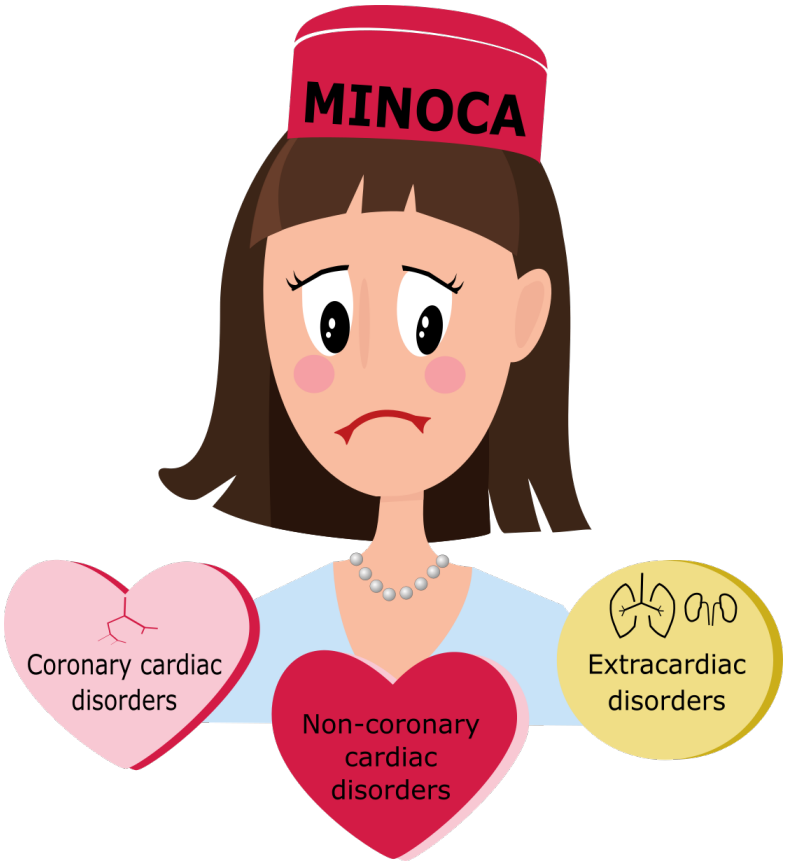
Table 1. Epidemiological studies in MINOCA

Study	Year	Type of study	Definition of coronary artery stenosis	Study group mean age	Study group female gender %	Prevalence of MINOCA %
Larsen et al	2005	Prospective cohort study	≥50%	58	40	4.6
Bugiardini et al	2006	Retrospective cohort study	≥50%	57	52	9.1
Patel et al	2006	Retrospective cohort study	≥50%	59	57	8.6
Gehrie et al	2009	Cohort Study	≥50%	59	59	10
Kang et al	2009	Prospective cohort study	≥50%	59	39	4.4
Planer et al	2014	Prospective cohort study	≥50%	54	53	8.8
Lindahl et al	2017	Register Study	≥50%	65	61	4.8
Smilowitz et al	2017	Register Study	≥50%	54 for men 63 for women	62	5.9
Barr et al	2017	Prospective cohort study	≥50%	57	50	15

ETIOLOGY

The MINOCA syndrome comprises several underlying diagnoses that can be divided into coronary cardiac disorders, non-coronary cardiac disorders and extra-cardiac causes [20]. The condition is most likely multifactorial with a combination of two or more different mechanisms. For example, a disrupted plaque in a coronary segment causing vasospasm or myocarditis as a triggering cause for takotsubo syndrome (TS) [21,22]

Figure 1. The underlying pathophysiology of MINOCA is multifactorial



Coronary cardiac disorders

Plaque disruption

The term disruption means erosion, ulceration, rupture or intraplaque haemorrhage that may occur in non-obstructive coronary lesions or in normal portions of the coronary tree. Plaque disruption (PD) is included in type-1 AMI, even when no thrombus can be found, according to the Universal definition document of Myocardial Infarction [10]. PD seems to be common in MINOCA. Two independent studies using intravascular ultrasound (IVUS) identified PD or ulceration in about 40% of patients with MINOCA[21,23]. Plaque morphology and global plaque burden appear to be important factors for disruption [24]. Another cohort-study using IVUS concluded that no women with MINOCA and completely normal arteries was found to have PD [25]. The location of plaques was different compared to CHD and PD did not typically occur at the site of the largest plaque in the vessel. The disrupted plaques in that study were more fibrous or fibrofatty, were less outwardly remodelled and had a lower percentage plaque burden [25]. They concluded that other and better techniques with higher resolution such as optical coherence tomography (OCT) or integrated backscatter IVUS could characterize the PD sites better and in future studies this is needed especially in women with normal coronary arteries.

Coronary Artery Spasm

Coronary artery spasm (CAS), also known as vasospastic or variant angina (Prinzmetal angina), predominately occurs during rest and in the midnight to early morning hours. The patients are often younger with fewer classical cardiovascular risk factors and are more likely to have other vasospastic disorders such as Raynaud's syndrome and migraine headache [26]. The reported prevalence varies greatly across ethnic populations with a high prevalence in Asia and may also be different between cohorts due to difficulties in confirming the diagnosis because of daily or monthly variation of disease activity [27]. This can reflect a vascular smooth muscle hyperreactivity to endogenous or exogenous vasospastic substances such as ergonovine, cocaine but also due to hyperventilation or exercise [28]. Provocative spasm testing has demonstrated inducible spasm in 28% of patients with MINOCA within 6

weeks post AMI according to 8 studies and could therefore be one of the major pathophysiological mechanisms in MINOCA [4]. There are also cases of CAS and normal coronary arteries described in patients when using epinephrine during severe anaphylactic reactions [29]

Coronary microvascular dysfunction

Coronary microvascular dysfunction (CMVD) and microvascular spasm/angina (previous term: syndrome X) are also potential causes of MINOCA since elevated cardiac markers have been detected following spasm testing despite the absence of inducible large vessel spasm [30]. The prevalence of CMVD is thought to be more common among women and there are increased long-term risk of cardiovascular events[31]. The reason for this is not fully understood and remains debated. There are theories that women's higher prevalence of luminal plaque erosion may play a role for microembolization [32]. Also, different hormone factors, such as the loss of oestrogen, may have an impact and probably mediate CMVD through loss of nitric oxide (NO) [26]. The prevalence of CMVD in the general population is not established, as testing for CMVD is difficult/usually not performed. There is one study of 80 patients with AMI and non-obstructed coronary arteries on angiography who underwent invasive CMVD testing, showing a prevalence of 30% [33]. Coronary flow reserve (CFR) was measured in the same study which were lower in patients with suggested CMVD. CFR measures the myocardial blood supply and especially the ability of the coronaries to increase blood flow under stress. Local infusion of a vasodilating drug, such as adenosine or the reactive hyperaemic response can be used to assess CRF [34]. A sub-study of the Stockholm Myocardial Infarction with Normal Coronaries (SMINC) study could not confirm catecholamine (Dobutamine)-induced CMVD in patients with takotsubo syndrome (TS). However, a small but significant difference in CFR was described at low-dose Dobutamine infusion [35].

Coronary thromboembolism

The prevalence of coronary thromboembolism in MINOCA is thought to be low and perhaps this is due to lack of screening for inherited disorders. Thrombosis in AMI can arise due to emboli in plaque disruption or CAS. It can also be caused by hereditary thrombophilia disorders including Factor V Leiden thrombophilia, and Protein S and C deficiencies. Studies in patients

with MINOCA have reported a 14% prevalence of these inherited disorders [4]. Coronary emboli can arise from the mentioned thrombophilia disorders but also because of other hypercoagulable states such as atrial fibrillation and valvular heart disease [9].

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is defined as spontaneous separation of the coronary arterial wall that is unrelated to trauma and atherosclerosis. SCAD is considered a rare cause of AMI, constituting approximately 0.1%-4% [36]. SCAD is common in young women, more than 90% of cases are reported in women with ACS [26]. Predisposing factors are connective tissue disease and/or arteriopathy (most commonly fibromuscular dysplasia), physical and emotional stress, and changes in the intima-media composition due to hormones, pregnancy and delivery. Survival is good but major adverse cardiac events are frequent including recurrent SCAD [36].

Myocardial bridging

Myocardial bridging (MB) is a congenital abnormality characterized by the presence of an intramural course of a coronary artery that can give rise to systolic flow disturbances. According to a recent published meta-analysis the overall prevalence of MB was 19%, in autopsy studies 42%, in CT studies 22% and coronary angiography studies 6% [37]. The authors concluded that autopsy studies are the gold standard in evaluating the prevalence of MB and that high-resolution CT scanning of coronary arteries should be preferred over coronary angiography studies. It has usually been considered as a benign condition but there are studies suggesting a potential haemodynamic significance of MB and some, usually case reports, indicates a possible association between MB and various cardiac pathologies like AMI, left ventricular rupture, life-threatening arrhythmias, hypertrophic cardiomyopathy, apical ballooning syndrome or sudden death [38]. MB is suggested to be a possible underlying mechanism for MINOCA but a subset of the SMINC-study showed similar prevalence for MB in MINOCA, with or without takotsubo syndrome (TS), as in healthy controls [39].

Non-coronary cardiac disorders

Takotsubo syndrome

Many names have been used for TS, that was discovered in Japan three decades ago; broken-heart syndrome, takotsubo cardiomyopathy, apical ballooning or transient cardiomyopathy. Lately a consensus was reached to define a universal name, according to the term cardiomyopathy which should be avoided and TS is recommended [40]. TS is often but not always the result of severe stress. There are two main clinical subtypes; primary or secondary TS, depending on the clinical picture and the presence of a major medical condition triggering the TS episode [40]. The primary form is described as being caused by a physical or emotional stressful trigger or as occurring spontaneously. Potential co-existing medical conditions may be the predisposing risk factors but are not the primary cause of the exacerbation. The secondary form is caused in patients already hospitalized for other medical, surgical, anaesthetic, obstetric or psychiatric conditions. In these patients, sudden activation of the sympathetic nervous system or a rise in catecholamines can cause TS. Emotional triggers could be divorce, unexpected death of a loved one or troublesome family matters while severe acute illness such as severe sepsis, acute anxiety attack/panic disorder or acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD)[40].

The pathogenesis of TS is not well understood and probably it involves excess of catecholamines and endothelin-1, myocardial stunning and CMVD [41]. Endothelial dysfunction is an imbalance between vasoconstricting and vasodilating factors that might be an important link between stress and myocardial dysfunction in TS, since studies have shown that mental stress can induce endothelial dysfunction [42]. Pre-existing vascular dysfunction can thus increase the risk of TS and perhaps trigger the sympathetic nervous system [41].

The prevalence of TS in MINOCA varies but according to a recent review including 16 CMR studies that were performed within 6 weeks after admission, the prevalence was 16% [4]. TS often has a similar presentation as in AMI with ST-segment changes, elevation of cardiac markers, reversible heart failure with myocardial stunning and the absence of occlusive coronary arteries. TS predominately affects postmenopausal women (90%) and cardiac markers are lower compared to CHD [40]. The prognosis has previously been expected to be generally good but several studies have lately presented

opposite results [43]. A recent case-control study from the Swedish Coronary Angiography and Angioplasty Register (SCAAR) during 2009-2013 showed similar mortality in TS when compared with CHD [44]. Also, the International Takotsubo Registry (InterTAK registry), comprising 26 centres in Europe and the United States compared TS with CHD during 2011-2014 and found similar rates of severe in-hospital complications including shock and death [45,46].

There is no single universally accepted diagnostic definition of TS. The most widely used in clinical practice and research is the Mayo Clinic Criteria of TS from 2004 which was modified 2008 [47,48] and is based on expert consensus opinion. The criteria include: 1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present. 2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture 3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin. 4. Absence of pheochromocytoma and myocarditis. There are new diagnostic criteria suggested by the Heart Failure Association (HFA) of the ESC from 2015 that includes recovery of ventricular systolic function on CMR at 3-6 months follow-up, elevated NT-proBNP and cardiac troponins in the acute phase. Pheochromocytoma is also included as a secondary cause of TS.

There are also some studies suggesting routine measurement of other cardiac biomarkers, such as NT-pro-BNP and markers of stress like catecholamine and cortisone to differentiate TS from AMI. One study could demonstrate that patients with STEMI had lower NT-pro-BNP levels and greater elevations of troponin T and CK-MB, compared to the TS group. Catecholamine and cortisol levels were not elevated in patients of TS, suggesting that routine measurement of these stress hormones is unlikely to be of diagnostic value in clinical practice [49].

There are anatomical variants of TS, with three more common and several rare anatomical variants. The apical, with or without mid-left ventricular variant, is estimated to have of a prevalence of up to 80% (Figure 2), only mid-left ventricular of 10-15% (Figure 3) and inverted or basal of around 5% [40]. There are clinical challenges in differentiating TS from myocarditis and CHD and milder forms of TS with rapid recovery that are misdiagnosed probably also exist [47].

Figure 2. Classical takotsubo syndrome. Diastolic and systolic freeze frames from a left ventriculogram illustrating hyperdynamic basal contraction and akinesis of the mid and apical segments (arrows).

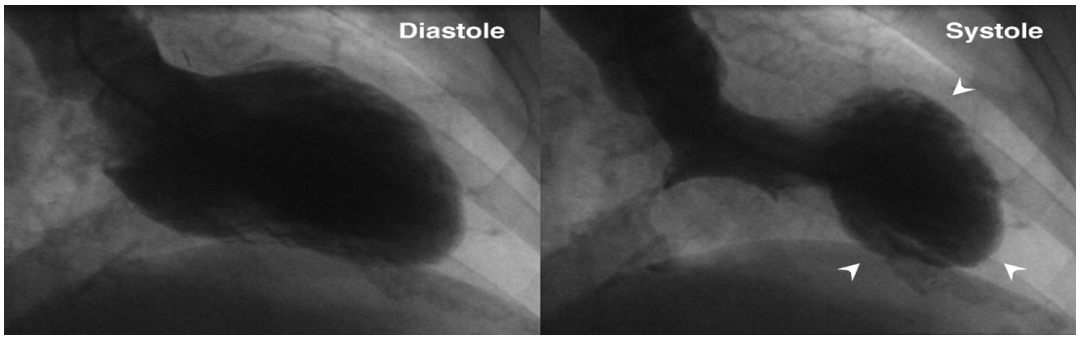
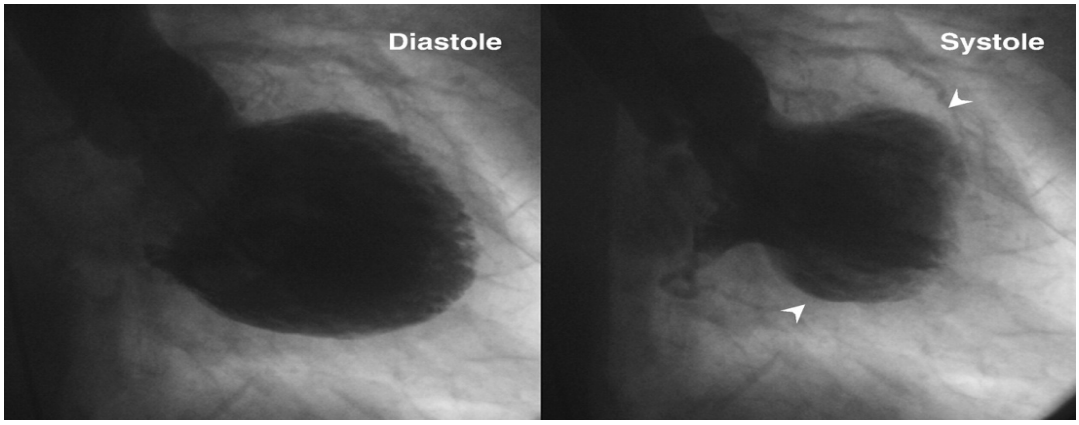


Figure 3. Only mid-left ventricular takotsubo syndrome. Diastolic and systolic freeze from a left ventriculogram with apical sparing variant of takotsubo syndrome. Function at the base and apex is preserved with akinesis of the mid segments (arrows).



Myocarditis

Myocarditis is common in MINOCA. The clinical presentation varies widely from one patient to another but often mimics the symptoms of AMI including ECG-changes and elevation of cardiac troponins. According to the 2013 ESC Task Force the definitive diagnosis can only be achieved by endomyocardial biopsy [50,51]. However, this is not a routine clinical practice and current guidelines recommend this only in a limited number of clinical cases that do not include common presentations of myocarditis, especially pseudoinfarction [52]. The aetiology often remains undetermined but a large variety of infectious and systemic diseases including drugs and toxins can cause myocarditis. Half of the patient with myocarditis recover within 4 weeks but the risk of developing persistent heart failure is 25% which can progress to end-stage dilated cardiomyopathy with a need of heart transplantation [50].

The prevalence depends on study design and is about 33% in MINOCA according to a recent meta-analysis of 5 studies [53]. The authors concluded that young age and high CRP were associated with myocarditis and they also highlighted the importance of using CMR in MINOCA to achieve the correct diagnosis and treatment. Another CMR study confirmed that myocardial fibrosis was more frequent in men and in patients younger than 40 and that the injury appears to be more regional and more severe in these cases [54].

Extracardiac disorders

Pulmonary embolism (PE) is often misdiagnosed as AMI with similar clinical presentation and with elevated cardiac troponins [55]. It is important to exclude PE with the help of D-dimer testing, computed tomography of the pulmonary arteries or ventilation/perfusion scintigraphy of the lungs [56]. There are also other conditions such as stroke, acute renal failure and adult respiratory distress syndrome that can be the cause for onset of MINOCA [57] .

Other forms of secondary AMI to consider includes anaemia, tachy-brady-arrhythmia, hypotension, shock, severe hypertension with or without LV hypertrophy, severe aortic valve disease, heart failure, cardiomyopathy, effects of toxins (e.g. sepsis) and pharmacological agents (e.g. catecholamines) [58]. Secondary or type 2 AMI is defined as myocardial cell necrosis due to supply-demand mismatch, characterized by significant increase and/or decrease in troponins with at least one value above the 99th percentile of a normal reference population in the absence of evidence for coronary plaque rupture in addition to at least one of the other criteria for AMI [10]. Factors of myocardial oxygen demand include systolic wall tension, contractility and heart rate while myocardial oxygen supply is conveyed by coronary blood flow and oxygen content. Type 2 AMI is a clinical challenge and lately often detected since more high-sensitivity cardiac troponin assays are used in the clinics [58]

CLINICAL CHARACTERISTICS

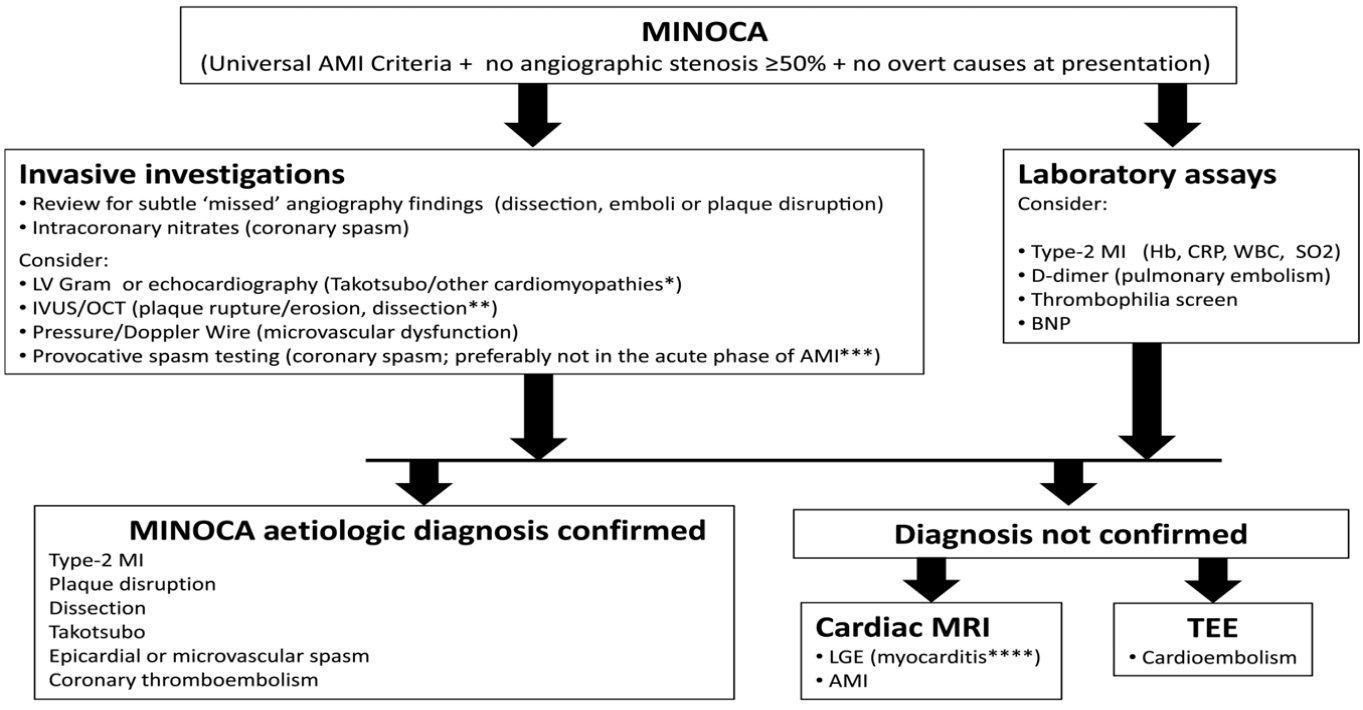
Patients with MINOCA are usually younger with different sex distribution including more women compared to patients with CHD. The cardiovascular risk factors in MINOCA are similar as in CHD except for a more favourable lipid profile [4]. Symptoms and ECG findings in this syndrome are similar regardless of underlying causes, and troponin markers tends to be lower

compared to CHD. The probability of MINOCA is similar between ECG with or without ST segment elevation for women, and lower in NSTEMI than STEMI among men [9]. A recent study revealed similar marital status, postsecondary education, work status, and household-income in patients with MINOCA as in patients with CHD [59].

CLINICAL MANAGEMENT

Lately several algorithms have been developed to help clinicians to assess MINOCA [4,60,61]. When coronary angiography shows no stenosis ≥ 50%, a left ventriculogram should be performed to describe the distributions of regional wall motion abnormalities. At this stage MINOCA should be handled as a "working diagnosis" [9]. PE should be excluded by using D-dimer testing and when there is further need of investigation by using computed tomography of the pulmonary arteries or ventilation/perfusion scintigraphy of the lungs. CMR is highly recommended in MINOCA and plays a crucial role in identifying myocarditis, areas of myocardial damage and other underlying causes. Myocarditis should be established early in the algorithm, maybe even before coronary angiography [9].

Figure 4. Recommended diagnostic algorithm for MINOCA



From: ESC working group position paper on myocardial infarction with non-obstructive coronary arteries Eur Heart J. 2016;38(3):143-153. doi:10.1093/eurheartj/ehw149

TREATMENTS AND SECONDARY PREVENTION IN MINOCA

Since MINOCA is not a disease but a clinical syndrome with different pathophysiological mechanisms there is no single treatment modality. A recent observational study indicated long-term beneficial effects on outcome in patients with MINOCA with statins and ACEI/ARBs and a trend toward positive effects of β-blocker and a neutral effect of dual anti-platelet therapy [17]. There is also experimental evidence that increased sympathetic activation is of importance for the occurrence of cardiovascular events, and therefore β-blocker treatment after AMI due to CHD might be beneficial [62]. In MINOCA patients, some authorities recommend treatment with β-blockers, mostly based on theoretical considerations [63]. On the other hand, some observational studies in patients with either cardiovascular risk factors only or known prior AMI, known CHD without AMI and in patients with TS have failed to show long-term beneficial effects of β-blocker treatment on cardiovascular events [46,64]. In the TS study mentioned above, the use of ACEI/ARBs was associated with improved survival at one year [46]. Generally, patients with MINOCA are discharged from the hospitals without any follow-up management. One recent study showed that achievement of secondary prevention targets such as blood pressure and LDL cholesterol levels, non-smoking and exercise training are associated with a prognostic benefit in patients with MINOCA similar to patients with CHD [65].

PROGNOSIS AND RECURRENT EVENTS

In general, the prognosis for patients with MINOCA is relatively good, with 12-month mortality around 5%, which is lower than in patients with CHD [4]. One study of 2 438 patients evaluating the long-term outcome of patients with MINOCA compared to CHD found a similar risk of major adverse cardiac event [66]. The authors concluded that patients with MINOCA remain at high risk of long-term recurrent ischemic events. Another study performed between 2011-2013 compared MINOCA that was classified as AMI type 1 with AMI type 2 and they found similar risk profiles, extent of necrosis and long-time prognosis regarding mortality risk [67].

The recurrence of the MINOCA syndrome has previously not been studied. There are some case reports of recurrent symptoms in patients with MINOCA, suggesting further investigation to define the cause and potential treatment of

symptoms [68]. Recently a study that followed 114 patients with TS during 2003-2015 confirmed recurrence of TS in seven cases (6.1%) and the time interval between the index event and its recurrence varied from six months to six years. Hypertension, COPD and/or asthma increased risk for relapse [69]. The authors concluded that TS recurrence should be the first differential diagnosis in patients with a history of TS. These findings are difficult to apply to all patients with MINOCA due to different underlying causes. On the other hand, since TS and CMVD are both known to reoccur one can speculate that this can appear in all cases.

MINOCA AND CMR IMAGING

CMR imaging has become an important tool in cardiology. The non-invasive technique is complex and newer therapeutic applications are constantly being developed. It can be used to assess ventricular volumes, masses and function. CMR can define cardiac anatomy and structure, quantify myocardial perfusion and measure blood flow [70]. The late gadolinium enhancement (LGE) technique images the myocardial tissues and can differentiate ischemic from non-ischemic causes of injury [71-73]. The contrast that is used in LGE is Gadolinium (Gd) which accumulates in the extracellular space. In fibrotic non-viable myocardium, the extracellular volume increases and the contrast accumulates and washes out slowly [73]. About ten minutes after contrast injection, an inversion recovery (IR) sequence is used to detect remaining contrast in the myocardium. In an infarcted area (scar) contrast media enhances the signal. Healthy myocardium has a low signal, if the correct IR-time is chosen [71,72]. CMR can differentiate between diagnoses included in MINOCA such as TS and myocarditis and can also establish if a sub-endocardial or transmural AMI has occurred[74].

One recent systemic review of 16 publications that performed CMR within 6 weeks after the event showed that an underlying diagnosis for MINOCA was found in nearly 80% of the cases. The results showed subendocardial infarction in 24% , myocarditis in 38%, TS in 16% and 21% patients with normal CMR [4]. There are several studies, mostly retrospective, that used CMR in MINOCA with similar results regarding myocardial infarction (16-26%) but great variation regarding myocarditis (27-54%) and normal cardiac MRI (0-30%) [74-82]. The time from coronary angiography to CMR is probably of importance and varied between 3-10 days in these studies (Table 2). There are some disadvantages with CMR such as long scanning time, and it is not feasible for

all patients for instance those with metal clips, cardiac devices and severe claustrophobia. The advantages of CMR are the non-invasive procedure, the use of non-toxic contrast agents and the three dimensional imaging capacity [70]

Table 2. CMR studies and the detection of underlying diagnosis in MINOCA

Study	Year of publication	Type of study	Patients included	Median time from angiogram to CMR (days)	CMR provides a diagnosis %
Laraudogoitia et al	2009	Retrospective	80	3	95
Leurent et al	2010	Prospective	107	5	90
Gerbaud et al	2011	Prospective	130	6	76
Chopard et al	2011	Prospective	87	10	63
Emrich et al	2015	Retrospective	125	3	90
Pathik et al	2016	Prospective	125	6	87
Camastra et al	2017	Retrospective?	190	4	85
Panovsky et al	2017	Retrospective	136	Lacking	92
Dastidar et al	2017	Retrospective	204	7	70

ATHEROSCLEROTIC AND INFLAMMATORY MARKERS IN HEART DISEASE

Biomarkers

There is evidence that inflammation contributes to the initiation and progression of atherosclerosis. High-sensitivity C-reactive protein (hsCRP) is an acute-phase reactant that measures subclinical systemic inflammation [83]. It is not clear whether inflammation simply is a result of the atherosclerotic process or if it is a major driver. Inflammation also gives raise to

dyslipidaemia with elevated low-density lipoprotein cholesterol (LDL-C), triglycerides and reduced high-density lipoprotein cholesterol (HDL-C). The cut-off point for hsCRP is challenging due to gender and racial/ethnic differences. For instance, African Americans have significantly higher hsCRP levels than white Americans and females have higher baseline levels than do men (43,44). In the large Jupiter study, patients with normal LDL-C and high hsCRP were treated with statin with reduction in cardiovascular events and 20% reduction in all-cause mortality [84,85]. The trial demonstrated that hsCRP was an independent risk factor for treatment with statin and was associated with significant lowering of hsCRP (37%).

Assessment of brain natriuretic peptides (BNP) is recommended by guidelines for diagnosis and management of patients with heart failure. BNP is a precursor secreted by myocytes during periods of increased ventricular stretch and wall tension. On secretion, the propeptide is split into the biologically active peptide and the more stable N-terminal fragment BNP (NT-proBNP) which is believed to be involved in the regulation of blood pressure, blood volume, and sodium balance [86]. We also know that NT-proBNP is a marker of vascular remodelling but it is unclear to what extent it can be used in prediction of CHD. The NT-proBNP is almost always significantly elevated during acute TS and some evidence suggests that NT-proBNP is a more useful diagnostic biomarker than troponin [87]. Therefore, elevated natriuretic peptide levels were included in the new diagnostic criteria for TS proposed by the HFA association of the ESC [40]. Recent published data also showed that admission NT-proBNP is an independent predictor for short and long-term adverse events in TS patients and could be used as a marker for risk stratification immediately at presentation [88,89].

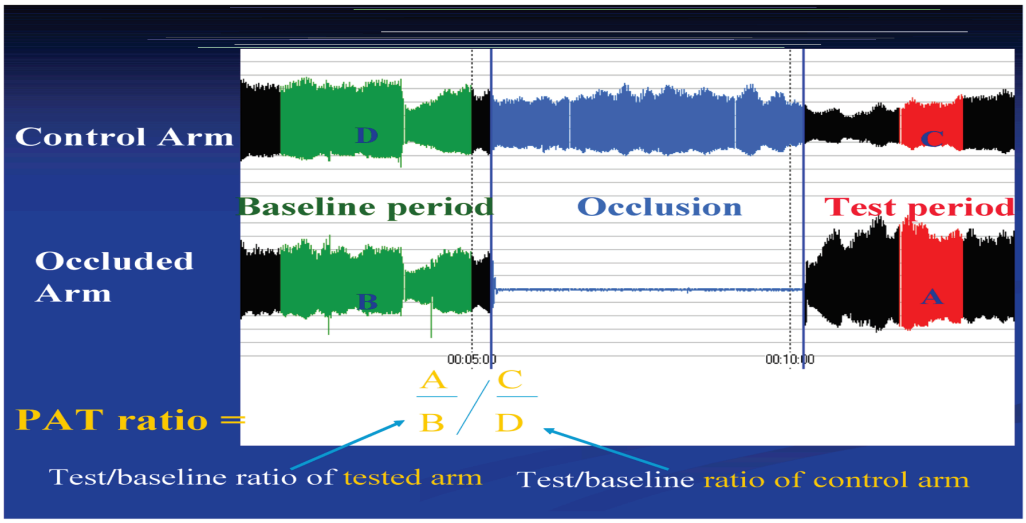
Non-invasive methods to measure early atherosclerosis.

Endothelial function

The endothelium is not a simple monolayer of cells separating flowing blood from the vascular wall, it is also important for the vascular homeostasis. NO is the principal mediator of endothelial function being a potent vasodilator, inhibiting platelet aggregation, vascular smooth muscle cell migration and proliferation, and monocytes adhesion. Cardiovascular risk factors promote the endothelial dysfunction which is described as impairment of vasodilation, plaque progression and vulnerability [90,91]. In the beginning endothelial function was measured invasively during cardiac catheterization [92]. Today, several non-invasive methods are used to measure reactive hyperaemia such as

brachial artery flow-mediated vasodilation of brachial artery (FMD) and endothelial peripheral arterial tonometry (Endo-PAT) [93]. The Endo-PAT technique is less operator-dependent and uses the contralateral arm as its internal control to correct for systemic changes during testing [94]. Both methods are based on the same principle of reactive hyperaemia phenomenon. That is, increased blood flow following a period of transient arterial occlusion, which serves as an index of endothelium-dependent vasodilator function (Figure 5). FMD assesses the endothelial response to shear stress in the brachial artery as a result of hyperaemia, whereas Endo-PAT measures the actual hyperaemia [94].

Figure 5. Typical recordings from the EndoPat.



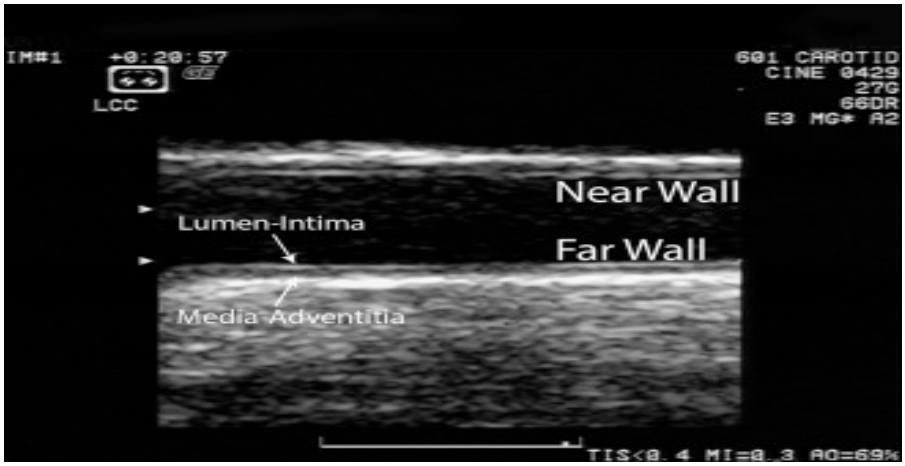
Estimation of peripheral arterial tonometry (PAT) ratio after correction of the reactive hyperaemia index for the control arm. Probe 1 corresponds to the occluded arm and probe 2 to the control arm. The blue-coloured interval corresponds to the duration of occlusion in the test arm.

Intima-media thickness

Another commonly used non-invasive method to measure early atherosclerosis is intima-media thickness (IMT). Previous studies have shown cross-sectional associations between IMT and cardiovascular risk factors, the prevalence of cardiovascular disease and the involvement of other arterial beds with atherosclerosis [95]. In the MESA (Multi-Ethnic Study of Atherosclerosis) study, IMT measurements were used as a surrogate for subclinical cardiovascular disease and as a variable predictive of cardiovascular events. IMT measurements of the common carotid artery were available in more than 99% of the MESA population and were predictive of cardiovascular events. More importantly, IMT and plaque thickness measurements made in the internal carotid artery and carotid bulb were also

available in more than 98% of the study group and plaques were strongly predictive of cardiovascular events [95].

Figure 6. An example of a common carotid artery image



The key interfaces used to measure common carotid artery intima-media thickness are the lumen-intima and the media-adventitia interfaces. The distance between these 2 interfaces is the intima-media thickness.

QUALITY-OF- LIFE IN PATIENTS WITH HEART DISEASE

Assessment of health-related quality-of-life (QoL) is an important and very useful health outcome especially in patients with chronic diseases like CHD and heart failure [96-98]. The definition of patient-reported outcome measurement (PROM) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patients response by a clinician or anyone else" [99]. The definition of QoL is more unclear and means different things to different people [100]. Universally accepted definition is up to date lacking. There is one suggested integrative definition of QoL that combines measures of human needs with subjective well-being or happiness. QoL is proposed as a multiscale, multi-dimensional concept that contains interacting objective and subjective elements. They related QoL to the opportunities that are provided to meet human needs in the forms of built, human, social and natural capital (in addition to time) and the policy options that are available to enhance these opportunities [101].

Patient-reported health status can be used as a complement to the traditional outcomes such as cost-of-care, hospitalization, cardiovascular events, mortality. QoL instruments can inform and evaluate the impact of a disease on general well-being, satisfaction with care and the benefits of medical interventions [96,102]. Despite this, surveys to assess patient-reported health status are underused in clinical practice [96].

When QoL is used in patients with CHD, it should comprise a disease-specific measure in addition to a generic measure [103,104]. The most widely used generic measures are the medical outcome study 36-Item Short-Form Health Survey (SF-36) and the Euro Quality of Life Scale (EQ-5D) and both are standardized and validated instruments. The most common disease specific instrument that is used in CHD is Seattle Angina Questionnaire (SAQ) [103].

Studies of patients with MINOCA and their QoL including control groups are lacking. However these patients are particularly vulnerable to anxiety and depression because few health providers offer psychological support or see such support as necessary when the results of a diagnostic procedure are not clinically significant [105]. Previously, low-vitality scores of SF-36 have been shown in chronic diseases such as chronic heart failure, where they were associated with fatigue and lower energy, readmission to hospital, inability to work, and negative outcomes, such as mortality [106]. In patients with CHD who underwent rehabilitation, low QoL was associated with greater fatigue and decreased exercise capacity, independent from mental distress and CHD severity score [107]. One recent review found that most cardiac rehabilitation programmes, education and counselling sessions, and other psychological and cognitive interventions improve QoL and exercise capacity in patients with CHD [7].

There are few studies on the long-term effects of uncertainty and associated health-related QoL in patients with heart disease. One study in patients with chest pain/angina waiting for elective angiography showed that high baseline uncertainty prior to angiography was associated with anxiety and depression and lower levels of perceived control and health-related QoL one year after coronary angiography, despite the angiographic findings and the treatment regimen [6]. They concluded that even a patient with normal coronary arteries is likely to experience marked reductions in QoL. A few studies have indicated that uncertainty is an important part of the experience of cardiac disease including those recovering from coronary-artery-bypass grafting or heart failure. In these studies higher levels of uncertainty correlated with lower QoL [108,109]. There is one study of interviews in 14 TS female patients at day one and 9 months after hospitalization pointing out the importance of early diagnosis to increase well-being. Initially patients struggled with confusion and insecurity concerning their diagnosis, future expectations, prevention, medical treatment and follow-up[110]. When the diagnosis of ACS was disapproved, a response of relief was expressed based on TS being a more favourable diagnosis, restoring certainty.

AIMS

The overall aim of this study is to identify the different underlying causes of MINCA with focus on prevalence and to describe risk factors including physical and mental health. The ambition is to better understand and handle this group of patients.

Hypotheses

1. CMR imaging can help us to separate different underlying causes of MINCA.

2. Patients with MINCA do not have generalized atherosclerosis.

3. Patients with MINCA have a poor QoL.

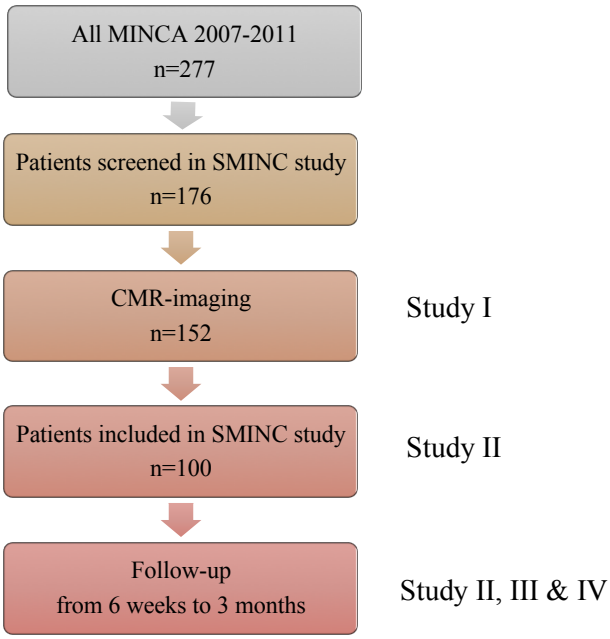
4. Patients with MINCA including TS have a high prevalence of anxiety and depression.

MATERIAL AND METHODS

DESIGN AND STUDY POPULATION

This thesis is based on one case-control study: the SMINC study. The study was ongoing for a period of four years (2007-2011) and all patients were screened at five coronary care units in the Stockholm metropolitan area (Figure 5). According to RIKS-HIA, the total number of patients with ACS in the same area at this time span was 4412.

Figure 7. Study flow chart in the SMINC study



The inclusion criteria were patients between 35 and 70 years of age fulfilling the diagnostic criteria of acute myocardial infarction, sinus rhythm on ECG and a coronary angiogram with no or minimal signs of atheromatosis. Minimal atheromatosis was defined as small irregularities in the coronary vessel wall, giving rise to <30% reduction of the vessel lumen with all coronary angiograms independently examined by a second angiographer. Acute myocardial infarction was diagnosed according to the ESC/ACC/AHA universal definition of myocardial infarction [10] and the diagnosis of TS was

based on the Mayo Clinic diagnostic criteria [47]. The exclusion criteria were patients with pacemaker, a previous myocardial infarction or cardiomyopathy, serum creatinine >150, previous and advanced chronic obstructive pulmonary disease, pulmonary embolism and myocarditis. Matching patients with CHD were recruited during their hospital stay or at follow-up at the respective coronary care unit. Healthy controls were recruited from the Swedish Population Registry (2007-2008) or from the computer-based medical record system Take Care® containing all citizens in Stockholm (2009-2012). The controls were selected randomly by date of birth and gender to match cases and contacted for participation by an invitation letter followed by a telephone call.

SCREENING-PHASE OF SMINC-STUDY

The first 100 patients underwent computed tomography (CT) of the pulmonary arteries to exclude PE. The case record form (CRF) protocol was changed to D-dimer testing after 100 negative CTs. CMR imaging was performed in 152 patients mainly to exclude myocarditis. After the screening-phase 100 patients with MINCA were included in the SMINC study and individually matched by gender and age to the two control groups. Symptoms, clinical findings and medication were registered in the CRF. The initial routine clinical chemistry and ECG were acquired from medical records and further blood-sampling was taken during follow-up 3 months after admission.

CMR imaging

CMR imaging protocol

The standard CMR imaging protocol included standard steady-state free precession (SSFP) cine imaging, T2-weighted oedema imaging and LGE for fibrosis detection. The protocol differed slightly between the different sites. The investigation was performed in the supine position with a cardiac coil using one of three 1.5 T systems (General Electric Healthcare; Signa Excite Twin-Speed, Waukesha, WI, USA; Siemens Sonata, Erlangen, Germany; and Philips Intera CV, Best, the Netherlands) during vector ECG monitoring. The imaging protocol included scout imaging, localization of the short axis and then covering of the whole left ventricle (LV) 1.6-3.3 ms, repetition time (TR) 2.8-3.6 ms, flip angle 60°, 25 phases, 8 mm slice, no gap, matrix 160–226 x 141–226 and T2-weighted triple inversion recovery (TE) 60–80 ms, TR two R–R intervals, TI 150–170 ms, slice thickness 8 or 14 (14 mm with GE

TwinSpeed), gap 8 mm, flip angle 90–180°, matrix 226–256 x 226–256) images were acquired in the same long- and short-axis planes. LGE images were acquired 15–20 min after contrast injection of intravenous gadolinium-DTPA (0.2 mmol kg-1) using a 2D or 3D (3D with Philips Intera CV) inversion recovery gradient echo sequence (TE 1.1–3.3 ms, TR 3.8–7.0 ms, inversion time 180–300 ms to null the signal of myocardium, 8 mm slice, no gap, matrix 240–256 x 180–192) in the same slice orientation as cine SSFP images. Each slice was obtained during end-expiratory breath holding. Two-, three- and four-chamber views were also obtained to confirm the findings.

CMR imaging analysis

All CMR images were analysed using offline, freely available segmentation software (SEGMENT V.1.8 R1405; http://medviso.com/segment.se/). The CMR images were examined and interpreted by two independent experienced experts blinded to all clinical data and the imaging report from the investigating hospital, thereby minimizing interhospital variation. In case of disagreement, a third CMR imaging specialist was consulted for consensus. End-diastolic and end-systolic volumes were measured in the phase with the largest and smallest LV volumes, respectively. LV ejection fraction, stroke volume and LV mass were calculated on cine SSFP sequences using manual delineation of the endocardial and epicardial borders including papillary muscles and trabeculations when contiguous with the LV. To calculate LVmass, the myocardial volume was multiplied by the density of myocardial tissue (1.05 g mL-1). All volumes were determined relative to body surface area. T2-weighted images were visually examined to detect areas of high signal compatible with oedema. LGE images were assessed for subendocardial enhancement in the distribution of a coronary artery suggesting myocardial infarction, or midwall/subepicardial enhancement suggesting myocarditis. Patients with patchy involvement on LGE (intramyocardial, including both subepicardial and subendocardial) were considered to have myocarditis. Images showing normal volumes and function and with no LGE or T2-weighted abnormalities were considered to be “normal CMR images”.

FOLLOW-UP MEETING IN SMINC-STUDY

During a follow-up visit 3 months after the acute event, several investigations were performed such as blood samples, non-invasive atherosclerosis measurements, bicycle stress test and completion of several surveys.

Laboratory tests

There were many different blood samples that were taken during the 3 months follow-up visit. In current thesis we will only focus on NT-proBNP.

NT-proBNP

Measurement of circulating levels of BNP or NT-proBNP has been recommended in the diagnosis and prognosis of patients with symptoms of left ventricular dysfunction and for stratification of risk in patients with AMI [111]. However there are some clinical conditions such as diabetes mellitus, obesity, renal insufficiency and anaemia that also can elevate NT-proBNP without established cardiovascular disease [86,111,112]. The cut-off or "normal" NT-pro-BNP is not clear but there are two studies in normal subjects without cardiovascular disease or LV-dysfunction that found increased levels with age and women (13,14).

Non-invasive measurements of atherosclerosis

Endothelial function test

Endothelial function was measured 3 months after the acute event with EndoPAT® (Itamar Medical Ltd), a specialized device for assessment of endothelial function. The system is based on peripheral arterial tone (PAT) signal technology; a non-invasive plethysmographic method measuring pulsatile volume changes in the digital bed. The test is user-independent and calculates automatically. The test was performed in a thermoneutral and quiet surrounding avoiding pre-test consumption of caffeine and smoking. The test quantifies endothelium-mediated changes in vascular tone elicited by a five-minute occlusion of the brachial artery using a standard blood pressure cuff inflated to a supra-systolic pressure. When the cuff is deflated, the surge of

blood flow causes an endothelium-dependent flow-mediated dilatation leading to reactive hyperaemia and an increase in the PAT signal amplitude. Values from the contralateral probe are used as a control for non-endothelial-dependent changes in vascular tone. The post-to-preocclusion ratio, called EndoScore or RHI, is calculated with specialized software [113,114] (Figure 5).

Intima-media ultrasound

Two-dimensional images of the left and right common carotid artery (CCA) were acquired, using an ultrasound scanner (Vivid 7; General Electric (GE), New York) equipped with a 12-MHz transducer, 3 months after the acute event. From each CCA, a long-axis cine loop of 3 beats and 3 diastolic images at the time of the ECG R-wave were stored digitally on magnet-optic discs for offline analysis. The IMT of the CCA far wall was measured in 3 diastolic images from each side using GE semiautomatic IMT analysis software. A 10-mm region of interest was manually placed starting 1 cm proximal to the carotid bulb. The intima media borders of the far wall, toward the lumen and the adventitia, were identified automatically by the program. Manual correction was not performed, and in the case of suboptimal tracking, the region of interest could be adjusted somewhat or another diastolic frame chosen. IMT was calculated as the mean of 3 semiautomatic measurements [115]. A mean of the results of IMT of the left and right CCA was calculated and used for comparison between the groups.

Exercise bicycle stress test

Patients with MINOCA and CHD controls performed a standardized exercise bicycle stress test 6-12 weeks after the acute event, whereas the healthy controls performed it at their one and only study visit. Subjects performed a symptom-limited exercise stress test using a modified protocol starting at 40 Watts (W) by addition of 10 W every minute. The test included an observation time of 10 minutes rest after the test to identify any possible post-stress symptoms and ECG changes including arrhythmias. During exercise, blood pressure, degree of subjective limitations like chest pain, effort, and breathless using the Borg score were monitored every minute. The predicted heart rate maximum was calculated using the traditional 220 minus age equation. Work capacity was measured in W, and results were presented as maximal work capacity and percentage of maximal heart rate.

Questionnaires measuring QoL, depression and anxiety

The SF-36 standard Swedish, version 1.0, was administered 3 months after the acute event in patients with MINCA and CHD controls and at the one and only study visit for the healthy controls [116]. SF-36 is a self-assessment health status questionnaire containing 36 items (questions) about sociodemographic, health, and personal behaviour, grouped into 8 multi-item domains, measuring the following: 1. physical functioning (10 items), 2. social functioning (2 items), 3. role limitations because of physical problems (4 items), 4. role limitations because of emotional problems (3 items), 5. mental health (5 items), 6. energy and vitality (4 items), 7. bodily pain (2 items), and 8. general health perception (5 items). Two summary measures, a physical component summary (PCS) score and mental component summary (MCS) score, are constructed from the 8 scales [117]. One single item inquired about change in health in the last year. Each of the scores for the domains were coded, and summed in an Excel chart, and later on transformed in the statistical program SPSS and the results presented from 0 (worst possible health) to 100 (best possible health).

The Beck depression inventory (BDI) and Hospital anxiety and depression scale (HADS) were administrated at the 3-month visit after the acute event, or at the first and only visit for the healthy controls. BDI and HADS are commonly used and validated screening tools for anxiety and depression in patients with AMI [118,119]. BDI is a 21 question multiple choice questionnaire that measures severity of depression [120]. There are three versions of BDI, the original BDI-I, the revised BDI-IA and the current version of BDI-II. In this study we used a Swedish version of BDI-I. Each question has four alternatives that are scored 0-4 points, giving a maximal score of 63 points. Scores can be categorized into normal (0-9), mild depression (10-18), moderate depression (19-29) and severe depression (30-63). Participants were asked to rate how they had been feeling for the last week.

We used the Swedish version of HADS that contains 14 items [121]. Seven of the items relate to anxiety (HADS-A) and seven relate to depression (HADS-D). Each question has four alternatives that are scored 0-3 points, giving a maximal score of 21 points on each subscale. Scores can be categorized into normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) anxiety/depression. Importantly the inventors created this survey to avoid somatic symptoms, such as pain, fatigue and insomnia that could interfere with the mental status. The subject are instructed to reply about their feelings during the past week [122].

STATISTICAL METHODS

Baseline data in all four studies are presented as mean ± standard deviation or median with interquartile range (IQR) in figures if numerical and as percent if categorical. Group-wise comparisons were made by Mann-Whitney u test (two groups) or Kruskal-Wallis (several groups) for continuous variables. A chi2 test was used for categorical data. A p-value < 0,05 was considered significant. For computations a software from IBM was used (SPSS statistics for Macintosh, versions 20 and 23.0 (IBM, Armonk, NY).

ETHICAL CONSIDERATIONS

For inclusion, patients were asked to give written informed consent. Each patient was assigned a study identification number and a record for identification was established. In the screening phase of the study 100 patients underwent CT of the thorax to exclude pulmonary embolism and all of them turned out to be negative. In this situation we did not find it ethical to proceed with further CT thorax due to risk of radiation and thus the protocol was changed to only primarily D-dimer. Discomfort during CMR examination is common and this was reduced by providing eye mask and music. Patients were also able to communicate if any discomfort appeared during the examination. If necessary, they also were given sedating medications to be able to perform the examination. The one´s with severe claustrophobia (9 patients) were excluded from the study. During the 3 month follow-up meeting we might have increased the stress for all our participants in the study by different non-invasive tests including different QoL surveys that took time to fill out. In addition, some of the participants could have experienced painful moments and fear during the withdrawal of blood samples and during the five minute occlusion of one arm when measuring the endothelial function. An experienced nurse and a doctor were available for help during the tests. We believe that the benefits of the study providing us with information about the MINCA population are greater than any potential risk of causing patients any discomfort.

RESULTS AND SPECIFIC DISCUSSION

STUDY I: Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study

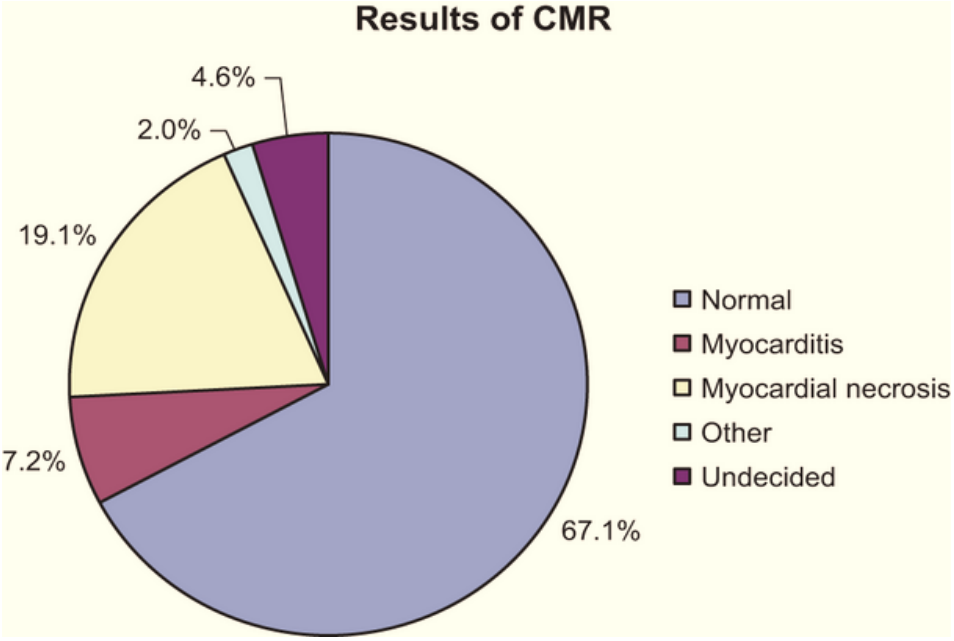
During the inclusion time that lasted between 2007 and 2011, 176 patients from the Stockholm metropolitan area with MINCA were screened. According to the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) 277 patients were found with MINCA in Stockholm during this period, meaning that 64 % of all patients with MINCA were included in the screening phase (Figure 7). The estimated prevalence of MINCA according to the number of ACS from RIKS-HIA during this time, was 6%, and most probably this is an underestimate since TS is not recorded as AMI.

CMR imaging results

A total number of 152 MINCA patients were able to undergo CMR. The remaining 24 patients did not undergo CMR due to lack of availability of magnetic resonance imaging (MRI), claustrophobia or other reasons.

In 102 MINCA patients CMR was found to be normal. Twenty-nine patients (19%) showed signs of myocardial necrosis and 11 (7%) had signs of myocarditis. There were also 10 cases of undetermined CMR findings (7%) (Figure 8). The CMR was performed a median of 12 days (6-28 days) after the acute event. In our study we found the underlying diagnosis in 26% of all CMR examinations. Among patients with a normal CMR, 33 (32%) patients were found to have a clinical diagnosis of TS including reversible LV dysfunction. As a result of using CMR-imaging the initial clinical diagnosis was changed in 65% of the cases.

Figure 8. Results of CMR imaging in MINCA



Compared with other CMR-studies in MINOCA (Table 2) that performed an earlier CMR with median time between 3-10 days, a smaller number of patients were able to get their underlying diagnosis (26% vs 70-90%). In these other studies, the rates of patients with myocardial necrosis and TS in MINOCA were similar to our study but with great variations in the rates of myocarditis and normal findings on CMR. Reasons for this could be that the CMR techniques and protocols has improved since our study was completed. We also excluded patients younger than 35 years which might be reflected in our lower rate of myocarditis compared to other studies (7% vs 38%). The poor harmony between the clinical and the CMR-based diagnosis (65%), as mentioned above, is in line with other CMR-studies in MINOCA. One study showed that 54% of the patients with MINOCA received a new diagnosis and 41% of them also had a management change after using CMR [79]. Our conclusion is that CMR is of great importance in the search of underlying diagnosis in patients with MINOCA. In addition, using CMR earlier after the event and with the latest techniques will most likely increase the number of patients in MINOCA with a correct diagnosis.

STUDY II: Risk factors and markers for acute myocardial Infarction with angiographically normal coronary arteries

A total number of 100 patients with MINCA were included into the SMINC-study. Patients with myocarditis were excluded by CMR (Figure 7). The mean age of all patients and controls was 58 to 59 years and women were predominant (72%). One quarter of the patients with MINCA (25%) fulfilled all Mayo Clinic diagnostic criteria for TS [47]. Another 19% had a less prominent abnormal ventricular wall motion on imaging with left ventriculography or echocardiography, indicating a possible TS in regression or a milder state. All patients with TS were women (Table 3).

Table 3. Baseline characteristics of MINCA compared to CHD and healthy controls.

	MINCA	CHD	Healthy control	MINCA vs CHD (p-value)	MINCA vs control (p-value)
Age (yrs)	58 ± 8	59 ± 8	59 ± 8	n.a.	n.a.
Women (%)	72	72	72	n.a.	n.a.
BMI (kg/m^2)	26 ± 5	27 ± 5	25 ± 4	***0.037***	0.557
Heart rate (bpm)	74 ± 15	75 ± 14	69 ± 15	0.706	n.a.
Systolic blood pressure (mm Hg)	147 ± 27	149 ± 27	128 ± 17	0.492	n.a.
Troponin ratio*	110 ± 176	275 ± 560	-	0.642	n.a.
CRP > 5 µg/L (%)	16	13	5	0.699	***0.010***
Smoker (%)	21	33	7	*0.056*	***0.004***
Ex-smoker (%)	29	34	40	0.447	0.102
Hypertension (%)	37	46	17	0.196	***0.001***
Hyperlipidaemia (%)	9	20	4	***0.027***	0.152
DM (%)	4	10	0	0.096	***0.043***
IGT and DM (%)	39	55	20	***0.029***	***0.004***
Migraine (%)	14	13	13	0.836	0.836
Thromboembolic disorder (%)	6	1	2	*0.054*	0.149
Inflammation (%)	30	20	10	0.102	***<0.001***
Psychiatric disorder (%)	20	11	3	0.079	***<0.001***
Triglyceride (mmol/L)	1.0 ± 0.5	1.4 ± 0.7	1.0 ± 0.6	***<0.001***	0.096
Cholesterol (mmol/L)	5.1 ± 1.0	5.4 ± 1.1	5.6 ± 1.0	0.092	***<0.001***
LDL-C (mmol/L)	3.0 ± 0.8	3.5 ± 0,9	3.6 ± 0.8	***0.002***	***<0.001***
HDL-C (mmol/L)	1.6 ± 0.5	1.3 ± 0.4	1.6 ± 0.5	***<0.001***	1.000

Values are mean ±SD. Significant p-values are indicated in bold fond.

Patients with MINCA had several established cardiovascular risk factors, mainly smoking, hypertension, impaired glucose tolerance (IGT) and diabetes mellitus (DM), inflammatory disease, and psychiatric disorders except for the lipid profile that was more favourable with low LDL and high HDL cholesterol (Table 3). These results are in line with a recent review of MINOCA patients except for the sex distribution, with more women in our study (72% vs 40%) [4]. The differences may reflect our exclusion criteria such as myocarditis and patients < 35 years of age. Previous data regarding sex differences in myocarditis are limited and diverse but there is one study revealing a higher prevalence and increased myocardial involvement in younger men [123].

A history of inflammatory disease was more common in patients with MINCA than in healthy controls, which is supported by the increase of C-reactive protein (CRP) at admission (Table 3). Hypercoagulability due to inflammation has been reported as a possible reason for MINCA. There are some case reports showing exacerbation of systemic inflammatory disease without evidence of vasculitis whereas others have identified secondary myocarditis due to vasospasm [124,125]. One recent observational study found that older age, diabetes mellitus, hypertension, smoking and increased plasma levels of CRP in MINOCA were associated with new major adverse cardiovascular events similar to CHD [126].

Table 4. Markers of atherosclerosis and myocardial dysfunction in patients with MINCA compared to CHD and healthy controls

	MINCA	CHD	Control	MINCA vs CHD	MINCA vs Control
Reactive hyperaemia (RHI) index	2.2 ± 0.7 %	2.1 ± 0.6 %	2.3 ± 0.6 %	p = 0.141	p = 0.639
Intima-media thickness (IMT) (mm)	0.71 ± 0.12	0.74 ± 0.16	0.70 ± 0.12	p = 0.216	p = 0.855
N-terminal pro brain natriuretic peptide (NT-pro-BNP)(ng/L)	133 ± 129	274 ± 460	68 ± 74	***p = 0.001***	***P < 0.001***

Bold value indicates p ≤ 0.05.

NT-proBNP measured 3 months after the acute event was lower in patients with MINCA than in CHD controls but greater than in the healthy control, group indicating remaining myocardial stress (Table 4). One can speculate if these results could reflect our larger proportion of MINCA with TS under recovery, since elevated level of NT-proBNP is obligatory in TS [40]. Other possible reasons could be other subgroups of MINCA with myocardial injury or coronary microvascular dysfunction [26,111] Unfortunately, we did not distinguish NT-pro-BNP between the different underlying causes for MINCA and NT-proBNP was not measured at admission for comparison. Also healthy women without cardiovascular disease are described with increased levels within the normal range of NT-pro-BNP [86]. Since our study material consisted of mainly women (72%) the higher NT-proBNP values in MINCA compared to healthy controls are difficult to interpret further.

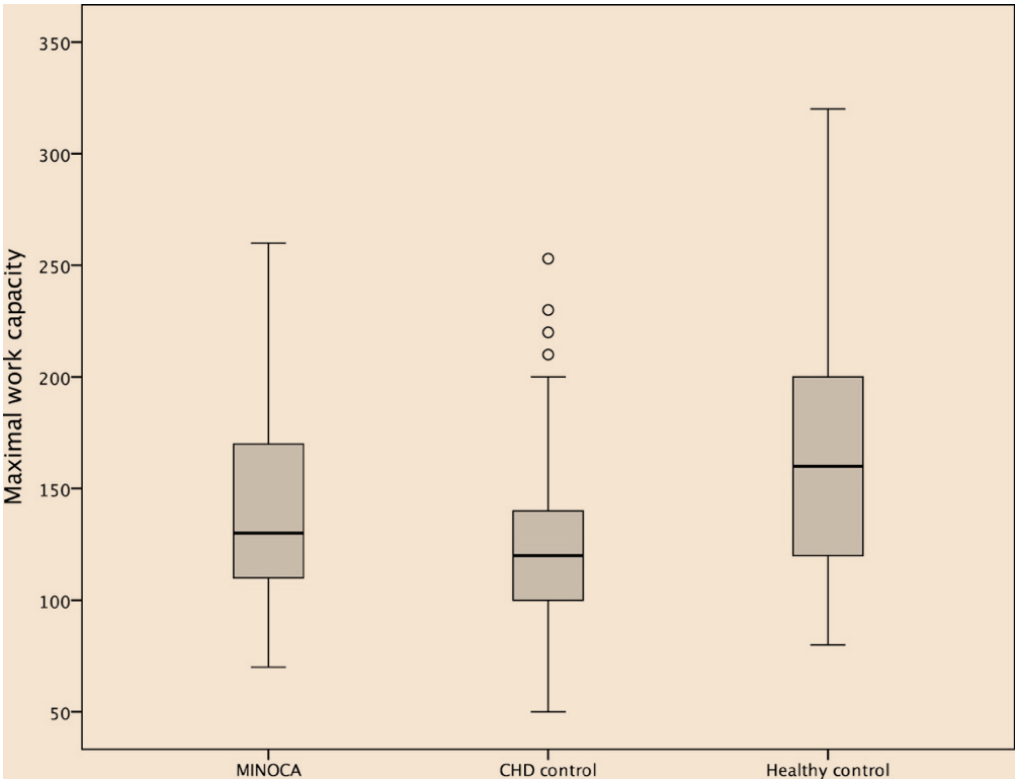
Regardless of similar cardiovascular risk factors, with the exception of the lipid profile, as in patients with CHD, the measurements of atherosclerosis (RHI and IMT) were similar to healthy controls and did not differ significantly compared to CHD despite an adequate power calculation. Perhaps this could be explained by the CHD control group that in our study was younger and included mainly STEMI with single vessel disease that represents patients with less atherosclerosis [127]. Also, since RHI was within the normal range for all groups one can discuss if certain medical therapies could have improved the endothelial function in our controls with CHD [128].

Our conclusion is that despite many classical cardiovascular risk factors for CHD, patients with MINCA do not have signs of early atherosclerosis. Further studies with larger groups are needed to clarify a potential difference regarding atherosclerosis burden in MINCA including a comparison with a group with more severe CHD.

STUDY III: Effect of myocardial infarction with nonobstructive coronary arteries on physical capacity and quality-of-life

The exercise stress test performed 6 weeks after admission in patients with MINCA showed lower work capacity compared to healthy controls (139 vs 167 W) and higher work capacity compared to patients with CHD (124 W) (Figure 9).

Figure 9. Work capacity in patients with MINCA and control groups



The percentage maximal heart rate was lower in patients with MINCA and CHD than in the healthy controls. Further analysis comparing patients with MINCA and healthy controls without β-blockers therapy showed similar difference in work capacity between the groups (126 W vs 171W).

Analysis of SF-36 performed 3 months after admission, showed that patients with MINCA had lower PCS and MCS scores compared to the healthy controls, including significantly lower values of all 8 domains. When comparing with CHD controls, we found lower vitality and mental health scores, whereas the rest of the dimensions were similar (Table 5).

Table 5. SF-36 dimensions and summary components in MINCA compared with control groups

SF-36 dimensions and summary components	MINCA n=90	CHD control n=91	Healthy control n=89	MINCA vs CHD control (p-value)	MINCA vs healthy control (p-value)
Physical function	83±21	82±19	94±11	0.500	**<0.001**
Role physical	77±37	78±35	94±21	0.932	**<0.001**
Body pain	68±29	74±28	83±22	0.157	**<0.001**
General health	65±22	68±21	82±17	0.301	**<0.001**
Vitality	55±23	64±25	73±20	**0.008**	**<0.001**
Social function	79±24	83±23	93±16	0.192	**<0.001**
Role emotional	71±41	76±39	94±22	0.384	**<0.001**
Mental health	69±19	74±22	82±15	**0.016**	**<0.001**
Physical Component summary (PCS) score	49±9	49±9	53±7	0.980	**<0.001**
Mental Component summary (MCS) score	43±12	47±12	51±8	**0.012**	**<0.001**

Values are mean ±SD. Significant p-values are indicated in bold fond font.

The MCS score was significantly lower in patients with MINCA compared to both control groups. This is supported by the rate of previous psychiatric disorders that was higher in MINCA (19%) compared to both the CHD (11%) and the healthy (3%) control groups. Our results might reflect our inclusion of a MINCA group that to a great extent consisted of patients with TS where emotional stress triggers are common [129]. In fact, more than half of the patients with MINCA (59%) recalled physical and/or emotional distress before admission indicating the influence of psychological factors in their illness. There is one recent study that measured baseline SF-12 in patients with MINOCA younger than 55 years. The physical functioning as described by the PCS score was similar to our findings but the mental functioning scores (MCS) were better (48.6) in patients with MINOCA [59]. The study did not use CMR imaging to exclude myocarditis which is reflected by the younger study group with less women (40%). Another explanation could be that our study consisted mainly of women in the menopausal status and that this condition is associated with higher rate of anxiety and depression symptoms [130]. We also know that depression and reduced exercise capacity are risk factors for poor prognosis in patients with CHD but the relationship between the two is unclear [131,132]. Our conclusion is that patients with MINCA do have physical and mental distress 3 months after the acute event, similar or worse to patients with CHD. Recognition and treatment of decreased QoL, will probably improve both physical and mental health in the same way as for other cardiac diseases.

STUDY IV: Prevalence of anxiety and depression symptoms in patients with myocardial infarction with non-obstructive coronary arteries

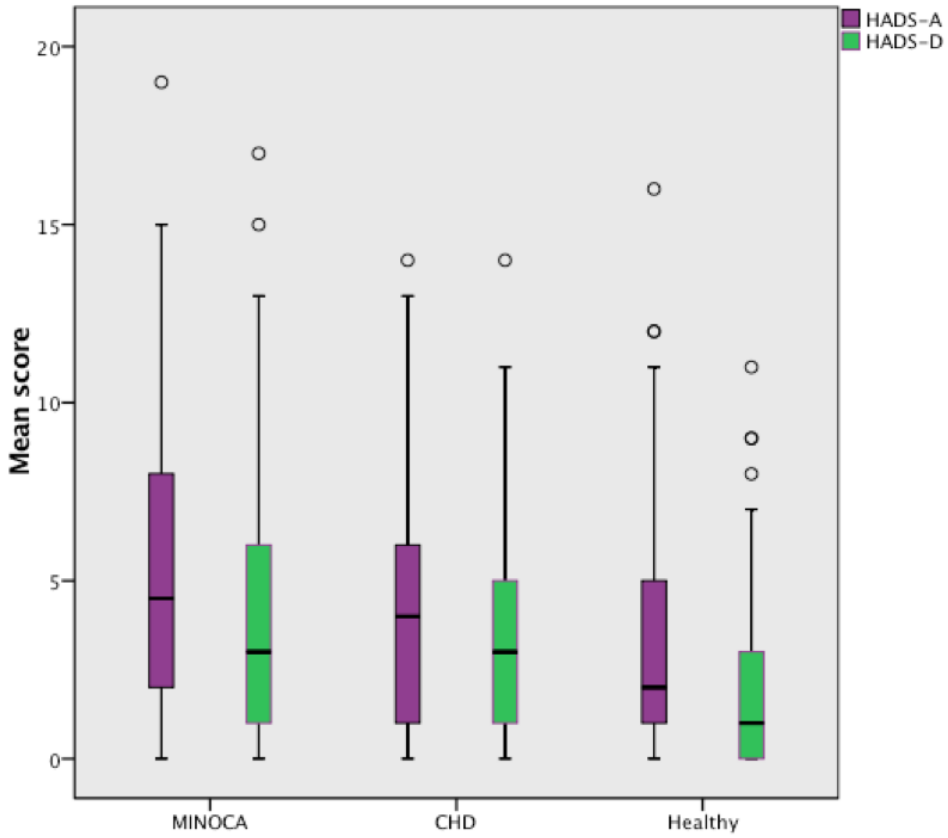
Patients with MINCA had higher scores on BDI compared with healthy controls and similar to CHD patients (Table 6). When using HADS-A, the score for anxiety was higher in MINCA compared with healthy controls and similar to CHD patients, and with HADS-D, the scores for depression were significantly higher in MINCA patients compared with healthy controls and similar to CHD patients (Table 6 and Figure 10).

Table 6. BDI and HADS scores in patients with MINCA compared with control groups

	MINCA	CHD	Healthy	MINCA vs CHD (p-value)	MINCA vs Healthy (p-value)
BDI	9.1±9.1	8.0±8.4	3.5±4.0	0.231	**<0.001**
BDI >=10	35 (35)	27(30)	9(9)	0.954	**0.006**
HADS	9.7±7.4	7.5±6.0	5.3±5.1	0.051	**<0.001**
HADS-A	5.5±4.3	4.2±3.4	3.3±3.3	**0.049**	**<0.001**
HADS-D	4.2±3.7	3.3±3.1	2.1±2.3	0.100	**<0.001**
HADS-A >=8	26 (27)	19 (21)	9 (9)	0.409	**0.002**
HADS-D >=8	17 (17)	12 (13)	4 (4)	0.467	**0.003**

N=99 for MINCA and N=90 for CHD relating to BDI, N=98 for MINCA and N=89 for CHD relating to HADS. N=97 for healthy control relating to BDI and HADS. Values are presented as mean ± standard deviation or number (percent).

Figure 10. Summary scores of the anxiety and depression subscales of HADS in patients with MINCA compared with control groups



Boxes indicate 25th percentile, median, and 75th percentile. MINOCA = Myocardial infarction with non-obstructive coronary arteries, CHD = Coronary heart disease, HADS = Hospital Anxiety and Depression Scale.

In our study, 25% had a definitive diagnosis of TS ,whereas another 19% had possible TS according to Mayo Clinic diagnostic criteria [47]. Patients with MINCA and TS had an increased prevalence of depression as measured by the BDI, similar mean scores for depression (HADS-D) and a higher mean score for anxiety (HADS-A) than patients with MINCA without TS. BDI is more sensitive regarding depression and compared to HADS-D often results in higher scores, possibly due to the inclusion of somatic symptoms which may have contributed to the result [118]. Our results are in line with a previous study that measured anxiety and depression, 3 months after the acute event in patients with TS with normal scores on the HADS-D (4.3) but increased scores on the HADS-A compared with controls with CHD [133].

Patients with MINCA also had a high prevalence of previous psychiatric diagnoses especially when diagnosed with TS, and more than half of them reported emotional and/or physical distress within one week before admission.

One may speculate whether the anxiety and depression in patients with MINCA and especially TS is a consequence of psychiatric comorbidity. A sensitivity analysis which excluded patients with previous psychiatric diagnosis, speaks against this by showing similar results between the control groups, except for the anxiety subscale of HADS when compared with healthy controls.

Furthermore, comparing HADS studies in patients with CHD, one study reported 38% with at least mild symptoms of anxiety (HADS-A >8) and 18% with mild symptoms of depression (HADS-D >8) during admission [134]. There were improvements in mean scores for anxiety and depression between admission and the 3-month assessment, but no further changes were observed at one-year follow-up [134]. Another study using HADS scores >8 in patients with a recent myocardial infarction, and the authors found 27% with anxiety and 13% with depression 6 weeks after the acute event where the results persisted at the 6-month follow-up [135]. These findings suggest 6 weeks up to 3 months as an optimal time to investigate for anxiety and depression.

Studies show that risk factors for CHD, such as smoking, hyperlipidaemia, physical inactivity and hypertension, are more common in patients with anxiety and there are also indications that anxiety is an independent risk factor for negative cardiac outcomes across many different cardiac diseases [136]. Depression in healthy persons without cardiac disease has been associated with future CHD and patients with anxiety during admission for a cardiac event are more likely to develop depression later on compared to patients without anxiety [137,138]. Since our studies reveal that patients with MINCA have similar cardiovascular risk factors and prevalence rates of anxiety and depression similar to patients with CHD, it may be assumed that these findings indicates a need for cardiac rehabilitation programmes in a comparable way to patients with CHD, to decrease the risk for cardiac events and to improve health and well-being.

GENERAL DISCUSSION

In this thesis, which was based on the SMINC-study, we were able to find some of the different underlying causes of MINCA, describe risk markers and evaluate the QoL. The different use of the terms MINCA and MINOCA in these studies might appear confusing. Previously, and when our SMINC-study started, the term MINCA was used and has lately been changed to MINOCA in order to use the same definition as the angiographic guidelines and to stress the fact that this syndrome also can occur in the presence of non-obstructive coronary lesions <50% stenosis [9]. Thus, in our studies patients with MINCA had a stricter definition of normal coronaries defined as <30% reduction of the coronary vessel wall and therefore our studies might have included more TS and myocarditis and excluded other diagnosis such as coronary spasm with or without plaque rupture/erosion. On the other hand we excluded patients with myocarditis in the screening phase and performed CT angiography in a subset of patients revealing that patients with MINCA and healthy controls were comparable regarding number of plaques[139].

The term MINOCA is not completely clear regarding underlying causes and prognosis and will most probably be revised for a better description and division of patients with ischemic-coronary and non-coronary disorders [140]. Recently troponin-positive non-obstructive coronary arteries (TpNOCA) has been proposed as a description of patients with a suspected AMI in the absence of obstructive CHD and the term MINOCA or maybe ischemia and non-obstructive coronary arteries (INOCA) is then reserved only for those who have evidence of ischemia-related myocardial necrosis [141].

CMR IMAGING IN MINCA

In our first study approximately half of the patients with MINCA reached a definite final diagnosis, 26% with CMR and the rest by using Mayo diagnostic criteria for TS [47]. Amongst patients considered to have normal findings on CMR-imaging, 33 (32%) were found to have typical signs of TS including reversible LV dysfunction. Of all patients screened with CMR imaging, 33 (22%) were found to have TS. In addition, there were also cases of suspected milder forms of TS or TS under recovery. The estimated incidence of TS in MINOCA varies between 1%-22% [47,74,82,142]. According to one CMR study in MINOCA, the time for CMR is crucial, especially in reversible conditions

such as myocarditis and TS [79]. The authors concluded the importance of performing CMR imaging early, preferably within 2 weeks after the acute event, which provides the possibility of detecting myocardial damage before healing occurs, thereby increasing the amount of correct diagnosis. In the same study CMR established a definitive diagnosis in 70% of patients with MINOCA and resulted in a change in the clinical management in 66 % of patients.

Previous studies shows that patients with MINOCA could be burdened with the unclarity of their diagnosis and it has been reported that patients are more disturbed about the uncertainty of diagnosis and fear of prognosis than the chest pain experienced [6,143]. Our findings highlight the importance of performing CMR in MINOCA, preferably with the latest T1 technique and at the right time for a better possibility of giving patients a correct diagnosis. With this approach we would be able to minimize the period of fear and uncertainty regarding the illness.

RISK MARKERS IN MINCA

The main result of the second study was that RHI and IMT were within the normal range in patients with MINCA indicating normal endothelial function. However, we were unable to demonstrate any differences compared to the CHD controls despite sufficient power of the study. Like in the review of Pasupathy et al patients with MINCA showed a similar cardiovascular risk factor profile as in patients with CHD, except for more favourable lipids [4]. There are some studies proposing that RHI and IMT in a younger population better assess coronary atherosclerosis than classical risk factors and probably are better markers of CHD risk [144]. Recent data showed that endothelial dysfunction was common in patients with TS, which can explain the theory of epicardial and/or microvascular coronary artery spasm in a similar way as in migraine or Raynaud´s phenomena [42,87,129]. These findings are contradictory to our findings with mainly patients with TS, normal endothelial function and a prevalence of migraine in MINOCA that was similar to the control groups (Table 3).

QUALITY-OF-LIFE, ANXIETY AND DEPRESSION IN MINCA

The third study showed similar dimensions in SF-36 with lower mental and vitality scores in MINCA compared to patients with CHD. The physical domain of SF-36 which comprises physical function, role-physical, bodily pain, and general health showed that patients with MINCA had similar scores compared with CHD controls which correlated well with the measured lower physical capacity when compared with the healthy controls. Recently, QoL data on CHD patients measured by the shorter SF-12 together with HADS confirmed similar findings as in our CHD controls compared with healthy controls with decreased PCS and MCS [145]. The authors concluded that the physical component of the SF-12 had a strong association with HADS and raised the question as to whether symptoms of anxiety and depression are an effect of the underlying physical condition. However, since patients with MINCA in our study did better on the exercise stress test than the CHD controls, their poor QoL cannot fully be explained by their exercise capacity. Our findings suggest that an acute overload of recent mental and/or physical stress with temporarily decreased myocardial function can explain the symptoms of fatigue and mental distress seen 3 months after the acute event.

The fourth study, measuring anxiety and depression scores showed both high and similar rates to patients with CHD. Patients with MINCA and TS scored higher for anxiety and depression than those without. These findings of a high prevalence of anxiety and depression in MINCA measured by BDI and HADS are in line with our findings with low QoL scores in MINCA. One study supports an association between HADS-D and QoL since patients with depression after myocardial infarction were more likely than those without to have poor QoL [146]. When comparing HADS subscales for anxiety and depression with SF-36 subscales, another study in patients with CHD found associations to all SF-36 subscales and most strongly to the mental health subscales indicating that the surveys measure similar aspects of mental health [147].

We know from previous studies that anxiety and depression in patients with CHD are associated with an increased risk of mortality and even more strongly if both conditions coexist [148,149]. There are many theories about the link between anxiety and depression and CHD, such as disturbances in the autonomic nervous system and hypothalamic-pituitary-adrenal axis that can increase sympathetic nerve activity and catecholamine secretion, causing

inflammation and platelet activation [150]. Depression is also associated with poor compliance with recommendations to reduce cardiovascular risk, such as quitting smoking, taking medications, exercising, and attending cardiac rehabilitation programs, which may lead to less optimal recovery and a worse prognosis [151].

The predominance of post-menopausal women with TS suggests that decreased oestrogen is a possible factor for increased mental stress with sympathetic activation and catecholamine release triggering coronary microvascular dysfunction as a possible pathophysiological mechanism [41]. From other studies, we have learned that middle-aged women have a high prevalence of both anxiety and depression, including panic attacks [150]. Epidemiologic studies also show that women are up to 40% more likely to develop mental health disorders than men [152]. The question remains whether the decline in mental health is a cause or consequence of MINOCA.

STRENGTHS AND LIMITATIONS

The strength of this study is the design with two types of age-and sex-matched controls and a detailed protocol that ensured strict exclusion of other conditions with similar symptoms, such as pulmonary embolism, myocarditis and other causes of type 2 myocardial infarction. On the other hand we used a stricter definition of what is considered MINOCA (<30% compared with <50% angiographic stenosis) and the results cannot, thus, be extrapolated to all patients with MINOCA.

One limitation was that CMR imaging was performed in a median of 12 days after the acute event and that the CMR imaging technique only included T2 sequences to detect oedema. The timing of CMR is of importance for the diagnosis of TS since the LV systolic dysfunction most often recovers within one week. The lack of intravascular imaging is also a limitation because it could have documented vulnerable plaques not visible on coronary angiography. However, CT angiography was performed in a subset of patients showing that patients with MINCA and healthy controls were comparable regarding plaque burden [139]. Another limitation is that a large number of patients with MINOCA received β-blockers. Despite the analyses of exercise capacity in patients without β-blockers, we cannot exclude the possibility that β-blockers might have influenced the overall results, including QoL. We used two different validated questionnaires (the BDI and HADS) measuring anxiety

and depression. The BDI is more sensitive for depression and, compared with the HADS-D, often results in higher scores, possibly because of the inclusion of somatic symptoms which may have contributed to our results [118]. The surveys cannot be used alone to diagnose anxiety and depression but are screening tools widely used for research purposes and only appropriate for use in case-control comparisons.

FUTURE STUDIES

The on-going SMINC-2 study in Stockholm Metropolitan Area where MINCA patients are investigated by CMR early after admission for MINCA (within 2-4 days) and with an updated CMR protocol and sensitive oedema sequences using T1 mapping [153]. In addition, a non-invasive coronary tomography angiography (CTA) is performed one month after the acute event to detect plaques not visible on coronary angiography and to exclude coronary dissection. The aim is to find >70% of underlying diagnoses with CMR in MINCA and compare them with historical results from the SMINC-1 study. The study is also collecting data on QoL over time (from admission to 12 months). All this will hopefully reduce the time of uncertainty and better describe recovery and well-being for our patients with MINCA.

After the initial coronary angiography, including left ventriculography, and CMR, future studies in MINOCA should consider further investigations to detect ruptured plaques, coronary dissections, microvascular dysfunction and coronary spasm, according to the position paper [9]. They suggested IVUS in connection with angiography and/or OCT as both can detect and characterize atherosclerotic plaques better than coronary angiography and coronary spasm provocation testing in cases of suspected coronary spasm. Laboratory test such as D-dimer to exclude pulmonary embolism, catecholamines to exclude pheochromocytoma, thrombophilia screening to exclude inherited causes of thromboembolism and NT-pro-BNP were also suggested.

A recently started multinational study (MINOCA-BAT) that will randomize >5600 MINOCA patients to treatment with oral ACEI/ARBs and β-blockers versus matching no treatment will examine rates of death and other cardiovascular events after one year. Participating countries are Australia, Norway, Sweden, UK and USA.

CLINICAL IMPLICATIONS

In connection with the CMR results from the screening-phase (Study I), our research group developed a protocol that has been used in Stockholm Metropolitan Area in order to use CMR routinely in patients with MINCA. After our main study we learned that patients with MINCA, despite similar cardiovascular risk factors as in patients with CHD, do not have any signs of early atherosclerosis measured by RHI and IMT. From this knowledge a basic treatment recommendation was given including aspirin and β-blockers, whereas other medications such as anti-platelet and lipid-lowering medications were excluded. This consensus was approved from expertise in this field. Meanwhile, we developed informative brochures about the MINCA syndrome, mainly for patients and their relatives. The third and fourth study confirmed our thoughts about reduced QoL and a high prevalence of anxiety and depression. In addition, during and after the SMINC study, patients with MINOCA were provided a yearly follow-up to increase our understanding and support for them.

CONCLUSIONS

CMR imaging is an important tool that can help us to identify the different underlying diagnoses in MINCA and enable a more appropriate treatment. Patients with MINCA do not have signs of early or generalized atherosclerosis and they share a number of cardiovascular risk factors with patients who have CHD, including high prevalence of anxiety and depression. There is also a decline in QoL similar to that of CHD patients and in some perspectives even worse in the domain of mental health. Altogether these findings show a high vulnerability to mental stress in patients with MINCA. The lack of clarity regarding diagnosis and treatment can also increase the stress and therefore highlight the need for a change in the management care of patients with MINCA, not only in the hospital but also after being discharged. Performing CMR early (2 weeks from presentation) and follow-up care in in a similar way as in patients with CHD will probably decrease the mental stress and improve QoL.

SVENSK SAMMANFATTNING

***Bakgrund*:** Hjärtinfarkt med normala kranskärl är ett vanligt tillstånd som främst drabbar medelålders kvinnor. Den bakomliggande orsaken är multifaktoriell och behöver utredas vidare för korrekt diagnos och behandling. Patienterna klagar ofta på brist av energi och verkar vara oroliga. Tidigare studier av MINCA (myocardial infarction with normal coronary arteries) patienter med kontrollgrupper saknades när Stockholm myocardial infarction and normal coronaries (SMINC) studien startade.

***Mål*:** Att beskriva resultaten från magnetisk resonanstomografi (MR) undersökning av hjärtat samt att beskriva bakgrunds karaktäristika, ateroskleros markörer och livskvalité (QOL) hos patienter med MINCA. Avsikten är att öka förståelsen och förbättra vården av denna grupp av patienter.

Specifika mål, /metoder och resultat:

Studie I: Syftet var att redovisa den verkliga förekomsten av myokardit och MINCA med eller utan hjärtinfarkt genom att använda MR undersökning av hjärtat. Resultaten visade att 67% av MINCA patienterna hade ett normalt fynd på MR hjärta, 19 % hade tecken på hjärtmuskelskada och 7% hade tecken på myokardit. Förekomsten av takotsubo syndrom (TS) i fallen med normal MR hjärta var 22 % vid användning av Mayo klinikens kriterium för TS. MR hjärta genomfördes i medeltal 12 dagar (6-28 dagar) efter insjuknandet.

Studie 2: Syftet var att beskriva riskfaktorer genom att analysera CRF (clinical research form) samt undersökningar som genomfördes i samband med återbesöket 3 månader efter insjuknandet hos patienter med MINCA och jämföra dessa med kontrollgrupper. Undersökningar som genomfördes var blodprover, mätning av RHI (reactive hyperemia index) och IMT (intima-media thickness) genom att använda EndoPAT® (Itamar Medical Ltd) och ultraljud av halsartärer. Resultaten visade att patienter med MINCA har en likartad riskfaktorprofil som hos patienter med kranskärlssjukdom med undantag för en mer gynnsam lipidprofil. Den aterosklerotiska graden mätt som RHI och IMT var inom det normala intervallet hos patienterna med MINCA och likartade jämfört med båda friska och kranskärlssjuka kontroller. En bakomliggande psykiatrisk sjukdom var vanligare hos patienter med MINCA och TS än de utan TS och mer än hälften av alla MINCA patienter uppgav fysisk och emotionell stress i samband med insjuknandet.

Studie 3: Syftet var att beskriva den fysiska arbetsförmågan och livskvaliteten från 6 veckor till 3 månader efter insjuknandet hos patienter med MINCA jämfört med kontroller genom att använda arbetstest på cykel och Short Form (SF)-36. Resultaten visade att patienter med MINCA hade en lägre fysisk arbetsförmåga och livskvalitet jämfört med friska kontroller. MINCA patienterna hade en något bättre arbetsförmåga jämfört med kranskärlssjuka kontroller men fick lägre poäng i den mentala komponenten av SF-36, i övrigt var dimensionerna likartade.

Studie 4: Målet var att undersöka den psykiska hälsan hos patienter med MINCA och jämföra dem med kontrollgrupper genom att använda två olika frågeformulär 3 månader efter den akuta händelsen; Beck Depression Inventory (BDI) och Hospital Anxiety and Depression scale (HADS). Resultaten visade att ångest och depression är vanligt med en prevalens som liknar patienter med kranskärlssjukdom. Ångest är vanligare hos patienter med MINCA och TS än de utan TS.

***Slutsats*:** MR hjärta är ett viktigt instrument som kan hjälpa oss att identifiera de olika underliggande diagnoserna i MINCA syndromet vilket möjliggör en mer adekvat behandling. Patienter med MINCA har inga tecken på tidig eller generaliserad ateroskleros trots en likartad riskfaktorprofil som hos patienter med kranskärlssjukdom inklusive hög prevalens av ångest och depression. Det har även en likartad försämring av livskvaliten som hos patienter med kranskärlsjukdom och i några avseende även sämre i domänen för mental hälsa. Osäkerheten kring diagnos och behandling kan även öka stressen vilket betonar behovet av en förändring när det gäller omhändertagandet av MINCA patienterna, inte bara på sjukhuset men även efter utskrivningen. MR hjärta på ett tidigt stadium (<2 veckor från insjuknandet) och en uppföljning på samma sätt som hos de kranskärlssjuka kommer troligtvis kunna minska den mentala stressen och förbättra livskvaliten.

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